

What is claimed is:

1. A host cell, comprising:

a) a first nucleic acid comprising a first promoter operably linked to a first polynucleotide wherein the polynucleotide comprises a sequence encoding an exogenous G protein-coupled receptor (GPCR); and

b) a second nucleic acid comprising a promoter operably linked to a second polynucleotide wherein the second polynucleotide comprises a sequence encoding a cyclic nucleotide-gated (CNG) channel selected from the group consisting of a wildtype CNG channel which is heteromeric and a mutant CNG channel comprising at least one mutation that makes the channel more sensitive to cAMP than a channel that does not comprise the mutation.

2. A cell according to claim 1, wherein the GPCR is not normally expressed in the cell.

3. A host cell according to claim 1, wherein the first nucleic acid and the second nucleic acid are part of one molecule.

4. A host cell according to claim 1, wherein the first nucleic acid and the second nucleic acid are part of different molecules.

5. A host cell according to claim 1, wherein at least one of the first and second nucleic acids are selected from the group consisting of viruses and plasmids.

6. A host cell according to claim 1, wherein at least one of the first and the second nucleic acids is part of the genome of the cell.

7. A host cell according to claim 1, wherein at least one of the first and the second nucleic acids is not part of the genome of the cell.

8. A host cell according to claim 1, wherein the host cell is a mammalian cell.

9. A host cell according to claim 8, wherein the cell is selected from the group consisting of BHK cells, mouse L cells, Jurkat cells, 153DG44 cells, HEK cells, CHO cells, PC12 cells, human T-lymphocyte cells and Cos-7 cells.

10. A host cell according to claim 1, wherein the cyclic nucleotide-gated channel is a mutant CNG channel and comprises at least two mutations that make the channel more sensitive to cAMP than a channel that does not comprise the mutations.

11. A host cell according to claim 10, wherein the cyclic nucleotide-gated channel is a mutant CNG channel and comprises at least three mutations that make the channel more sensitive to cAMP than a channel that does not comprise the mutations.

12. A host cell according to claim 1, wherein the cyclic nucleotide-gated channel is encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS:1, 3, 5, and 7.

13. A host cell according to claim 1, wherein cyclic nucleotide-gated channel comprises a sequence selected from the group consisting of SEQ ID NO:2, 4, 6, and 8.

14. A host cell according to claim 1, wherein cyclic nucleotide-gated channel comprises a sequence selected from the group consisting of the CNG channels whose sequences are provided in figures 8 and 9.

15. A cell according to claim 1, wherein the first polynucleotide comprises a sequence encoding a full length G protein-coupled receptor.

16. A host cell according to claim 1, wherein the first polynucleotide comprises a sequence encoding a mutated G protein-coupled receptor.

17. A host cell according to claim 16, wherein the first polynucleotide comprises a sequence encoding a truncated G protein-coupled receptor.

18. A cell according to claim 1, further comprising a third nucleic acid comprising a third promoter operably linked to a third polynucleotide wherein the third polynucleotide comprises a sequence encoding a G protein that interacts with the GPCR encoded by the first nucleic acid.

19. A cell according to claim 18, wherein the G protein is a promiscuous G protein.

20. A cell according to claim 19, wherein the G protein is selected from a group consisting of G<sub>s</sub>, G<sub>i</sub>, G<sub>q</sub>, G<sub>olf</sub>, G<sub>o</sub>, and G<sub>12</sub>.

21. A cell according to claim 1, wherein the G protein-coupled receptor substantially interacts with at least one G protein selected from the group consisting of G<sub>s</sub>, G<sub>i</sub> or G<sub>q</sub>.

22. A method of detecting activity of a GPCR, comprising:

(a) expressing the GPCR in a cell from an exogenous nucleic acid molecule;

(b) expressing a cyclic nucleotide-gated (CNG) channel selected from the group consisting of a wildtype CNG channel which is heteromeric and a mutant CNG channel comprising at least one mutation that makes the channel more sensitive to cAMP than a channel that does not comprise the mutation; and

(c) measuring activity of the channel wherein activity of the channel indicates activity of the GPCR.

23. A method according to claim 22, wherein the CNG channel is expressed from an exogenous nucleic acid.

24. A method according to claim 22, wherein the CNG channel is expressed from the genome of the cell.

25. A method according to claim 22, wherein measuring comprises the use of a dye or probe.

26. A method according to claim 25, wherein the dye or probe is a fluorescent dye or probe that can be detected by UV-based imaging systems.

27. A method according to 25, wherein the dye is a  $\text{Ca}^{2+}$  sensitive dye or probe.

28. A method according to 25, wherein the dye is a voltage sensitive dye or probe.

29. A method according to claim 22, wherein measuring comprises determination of activation of CNG channel activity in a single cell.

30. A method according to claim 29, wherein activation is determined by UV-based fluorescence using a microscope.

31. A method according to claim 30, wherein the microscope is coupled to a computer system.

32. A method according to claim 31, wherein the computer system tracks individual cells and performs statistical analysis.

33. A method according to claim 22, wherein measuring is performed with a multiwell microplate reader.

34. A method according to claim 33, wherein the reader is a fluorometric-based reader with a CCD camera.

35. A method according to claim 33, wherein the reader is a fluorometric-based scanning microplate reader.

36. A method according to claim 22, further comprising attaching the cell to a solid surface.

37. A method according to claim 36, wherein the solid surface is selected from the group consisting of slides and multiwell plates.

38. A method according to claim 22, wherein the cell is pretreated with a cAMP analogue before measuring.

39. A method according to claim 22, wherein the cell further expresses a promiscuous G protein.

40. A method according to claim 22, wherein measuring comprises determining ion flux.

41. A method according to claim 40, wherein ion flux is determined by a change in spectral characteristic of a dye or probe.

42. A method according to claim 40, wherein ion flux is determined by patch clamp.

43. A method of identifying a ligand for a receptor, comprising:

(a) contacting a cell with a compound wherein the cell expresses the receptor and at least one cyclic nucleotide-gated (CNG) channel, wherein the receptor is not endogenous to the cell and the CNG channel is selected from the group consisting of a wildtype CNG channel which is heteromeric and a mutant CNG channel that has been engineered to increase the channel sensitivity to cAMP; and

(b) measuring activation of the CNG channel, wherein activation of the CNG channel indicates that the compound is a ligand for the receptor.

44. A method according to claim 43, wherein the CNG channel is expressed from an exogenous nucleic acid.

45. A method according to claim 43, wherein the CNG channel is expressed from the genome of the cell.

46. A method according to claim 43, wherein measuring comprises the use of a dye or probe.

47. A method according to claim 46, wherein the dye or probe is a fluorescent dye or probe that can be detected by UV-based imaging systems.

48. A method according to 46, wherein the dye or probe is a  $\text{Ca}^{2+}$  sensitive dye or probe.

49. A method according to 46, wherein the dye or probe is a potential sensitive dye or  
5 probe.

50. A method according to claim 43, wherein measuring comprises determination of  
activation of CNG channel activity in a single cell.

10 51. A method according to claim 50, wherein activation is determined by UV-based  
fluorescence using a microscope.

52. A method according to claim 51, wherein the microscope is coupled to a computer  
system.

15 53. A method according to claim 51, wherein the computer system tracks individual cells  
and performs statistical analysis.

20 54. A method according to claim 43, wherein measuring is performed with a multiwell  
microplate reader.

55. A method according to claim 54, wherein the reader is a fluorometric-based reader  
with a CCD camera.

25 56. A method according to claim 55, wherein the reader is a fluorometric-based scanning  
microplate reader.

57. A method according to claim 43, further comprising attaching the cell to a solid  
surface.

30 58. A method according to claim 57, wherein the solid surface is selected from the group  
consisting of slides and multiwell plates.

59. A method according to claim 43, wherein the cell is pretreated with a cAMP analogue before being contacted with the ligand.

60. A method according to claim 43, wherein the cell further expresses a promiscuous G  
5 protein.

61. A method according to claim 43, wherein measuring comprises determining ion flux.

62. A method according to claim 61, wherein ion flux is determined by a change in  
10 spectral characteristic of a dye or probe.

63. A method according to claim 61, wherein ion flux is determined by patch clamp.

64. A method of identifying an agent that modulates an activity mediated by a GPC  
15 receptor comprising:

(a) contacting a cell with the agent and a ligand for the receptor wherein the cell expresses the receptor and at least one cyclic nucleotide-gated (CNG) channel selected from the group consisting of a wildtype CNG channel which is heteromeric and a mutant CNG channel that has been engineered to increase the channel sensitivity to cAMP;

(b) measuring activation of the CNG channel.  
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65. A method according to claim 64, further comprising:

(c) comparing activation of the CNG channel to activation of the channel in the absence of the agent, wherein a difference in activation of the CNG channel indicates the  
25 agent modulates the activity.

66. A method according to claim 64, wherein the CNG channel is expressed from an exogenous nucleic acid.

30 67. A method according to claim 64, wherein the CNG channel is expressed from the genome of the cell.

68. A method according to claim 64, wherein measuring comprises the use of a dye or probe.

69. A method according to claim 68, wherein the dye or probe is a fluorescent dye or probe that can be detected by UV-based imaging systems.

70. A method according to 69, wherein the dye or probe is a  $\text{Ca}^{2+}$  sensitive dye or probe.

71. A method according to 69, wherein the dye or probe is a potential sensitive dye or probe.

72. A method according to claim 64, wherein measuring comprises determination of activation of CNG channel activity in a single cell.

73. A method according to claim 72, wherein activation is determined by UV-based fluorescence using a microscope.

74. A method according to claim 73, wherein the microscope is coupled to a computer system.

75. A method according to claim 74, wherein the computer system tracks individual cells and performs statistical analysis.

76. A method according to claim 64, wherein measuring is performed with a multiwell microplate reader.

77. A method according to claim 76, wherein the reader is a fluorometric-based reader with a CCD camera.

78. A method according to claim 76, wherein the reader is a fluorometric-based scanning microplate reader.



79. A method according to claim 64, further comprising attaching the cell to a solid surface.

80. A method according to claim 79, wherein the solid surface is selected from the group  
5 consisting of slides and multiwell plates.

81. A method according to claim 64, wherein the cell is pretreated with a cAMP analogue before being contacted with the ligand.

10 82. A method according to claim 64, wherein the cell further expresses a promiscuous G protein.

83. A kit comprising a container containing a cell according to claim 1.

15 84. A kit according to claim 83, further comprising at least one reagent selected from a group consisting of buffers, salts and dyes.

85. A kit according to claim 84, further comprising at least one dye selected from a group consisting of voltage sensitive dyes and Ca sensitive dyes.

20 86. A method of detecting activity of a GPCR , comprising:  
(a) expressing the GPCR in a cell from an exogenous nucleic acid molecule; and  
(c) measuring activity of a CNG channel wherein activity of the channel indicates activity of the GPCR.

25 87. A method according to claim 86, wherein the CNG channel is expressed from an exogenous nucleic acid.

30 88. A method according to claim 87, wherein the CNG channel is expressed from the genome of the cell.

89. A method according to claim 87, wherein the CNG channel comprises at least one mutation that makes the channel more sensitive to cAMP.

90. A method of identifying a ligand for a receptor, comprising:

(a) contacting a cell with a compound wherein the cell expresses the receptor and at least one cyclic nucleotide-gated (CNG) channel; and

(b) measuring activation of the CNG channel, wherein activation of the CNG channel indicates that the compound is a ligand for the receptor.

91. A method according to claim 90, wherein the CNG channel is expressed from an exogenous nucleic acid.

92. A method according to claim 90, wherein the CNG channel is expressed from the genome of the cell.

93. A method according to claim 90, wherein the CNG channel has been engineered to increase the channel sensitivity to cAMP.

94. A method according to claim 90, wherein the receptor is expressed from an exogenous nucleic acid.

95. A method according to claim 90, wherein the receptor is expressed from the genome of the cell.

96. A method of identifying an agent that modulates an activity mediated by a GPC receptor comprising:

(a) contacting a cell with the agent and a ligand for the receptor wherein the cell expresses the receptor and at least one cyclic nucleotide-gated (CNG) channel; and

(b) measuring activation of the CNG channel.

97. A method according to claim 96, further comprising:

(c) comparing activation of the CNG channel to activation of the channel in the absence of the agent, wherein a difference in activation of the CNG channel indicates the agent modulates the activity.

98. A method according to claim 96, wherein the CNG channel is expressed from an exogenous nucleic acid.

99. A method according to claim 98, wherein the CNG channel is expressed from the genome of the cell.

100. A method according to claim 96, wherein the CNG channel has been engineered to increase the channel sensitivity to cAMP.

101. A method according to claim 98, wherein the receptor is expressed from an exogenous nucleic acid.

102. A method according to claim 96, wherein the receptor is expressed from the genome of the cell.